Title

An integrated brain-behavior model for working memory.

Journal
Molecular psychiatry, 23(10)

ISSN
1359-4184

Authors
Moser, DA
Doucet, GE
Ing, A
et al.

Publication Date
2018-10-01

DOI
10.1038/mp.2017.247

Peer reviewed

HHS Public Access
Author manuscript
Mol Psychiatry. Author manuscript; available in PMC 2018 November 29.

Published in final edited form as:
Mol Psychiatry. 2018 October ; 23(10): 1974–1980. doi:10.1038/mp.2017.247.

An integrated brain-behavior model for working memory

Dominik A. Moser, Ph.D.[*,1], **Gaelle E. Doucet, Ph.D.**[*,1], **Alex Ing, Ph.D.**[2], **Danai Dima, Ph.D.**[3,4], **Gunter Schumann, M.D., Ph.D.**[2], **Robert M. Bilder, Ph.D.**[5], and **Sophia Frangou, M.D., Ph.D.**[1,‡]

[1]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

[2]Social Genetic & Developmental Psychiatry, Institute of Psychiatry, Psychology and Neurosciences, King's College, London WC2R 2LS, UK

[3]Department of Psychology, City University of London, London EC1V 0HB, UK

[4]Department of Neuroimaging, Institute of Psychiatry, Psychology and Neurosciences, King's College, London WC2R 2LS, UK

[5]Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine, University of California Los Angeles, CA 90095, USA

Abstract

Working memory (WM) is a central construct in cognitive neuroscience because it comprises mechanisms of active information maintenance and cognitive control that underpin most complex cognitive behavior. Individual variation in WM has been associated with multiple behavioral and health features including demographic characteristics, cognitive and physical traits and lifestyle choices. In this context, we used sparse canonical correlation analyses (sCCA) to determine the co-variation between brain imaging metrics of WM-network activation and connectivity and non-imaging measures relating to sensorimotor processing, affective and non-affective cognition, mental health and personality, physical health and lifestyle choices derived from 823 healthy participants derived from the Human Connectome Project. We conducted sCCAs at two levels: a global level, testing the overall association between the entire imaging and behavioral-health datasets; and a modular level, testing associations between subsets of the two datasets. The behavioral-health and neuroimaging datasets showed significant interdependency. Variables with positive correlation to the neuroimaging variate represented higher physical endurance and fluid intelligence as well as better function in multiple higher-order cognitive domains. Negatively correlated variables represented indicators of suboptimal cardiovascular and metabolic control and lifestyle choices such as alcohol and nicotine use. These results underscore the importance of accounting for behavioral-health factors in neuroimaging studies of WM and provide a

[‡]**Corresponding author:** Sophia Frangou, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, 1425 Madison Avenue, NY, NY 10029, USA, sophia.frangou@mssm.edu; Tel: +1-212-659-1668.
[*]These authors contributed equally to the manuscript.

Supplementary information is available at the MP website.

Financial Disclosures: The authors report no conflict of interest.

neuroscience-informed framework for personalized and public health interventions to promote and maintain the integrity of the WM network.

Introduction

Working memory (WM) is the ability to store, update and manipulate goal-relevant information[1,2]. WM operations engage multiple brain regions but they critically depend on the coordinated activity of a dorsal cortical network anchored in the dorsolateral prefrontal cortex (dlPFC), the parietal cortex (PAR) and the dorsal anterior cingulate cortex (dACC)[3–5]. Within this network, there is evidence of relative functional specialization according to process; the dlPFC is hypothesized to be involved in encoding, setting attentional priorities and manipulating information[6,7], the PAR in maintaining attentional focus and storing information[8,9] and the dACC in error detection and performance adjustment[10]. Regional activation within this network is load-dependent and responds to the demand for maintenance, updating and manipulation[4,11–13]. In addition to regional activation, the WM-network can be characterized by its functional and effective connectivity[14,15]. Functional connectivity represents the statistical dependence of regional changes in blood-oxygen-level-dependent (BOLD) signal[16] while effective connectivity models the influence that WM-network regions exerts over each other[17].

The study of WM is central to cognitive neuroscience because it supports other higher-order cognitive abilities (including but not limited to general fluid intelligence, learning, problem solving and decision making)[18], and lower-order mental operations that require cognitive control[19]. Individual variation in WM is influenced by multiple variables including age, level of education, personality traits[20–23], lifestyle choices[24] and physical health characteristics[22,25]. Additionally, WM deficits are a prominent feature of neurological[26] and psychiatric conditions[27] including psychotic, mood and anxiety disorders and neurodevelopmental and neurodegenerative disorders.

The inter-relationship between the function of the WM-network and its multiple behavioral and health correlates is of key translational importance but has not been adequately addressed because individual studies commonly focus on a limited number of imaging and behavioral variables. This represents a major drawback when making inferences about the nature of case-control differences in psychiatric neuroimaging as patients commonly differ systematically from controls on multiple behavioral variables that are not related to primary disease mechanisms[28].

In this context, we sought to quantify brain-behavior relationships with regards to WM using the unique dataset of the Human Connectome Project (HCP, www.humanconnectome.org). Smith and colleagues[29] have already demonstrated the value of this approach by defining the co-variation matrix between behavioral variables and resting-state connectivity measures derived from 461 HCP participants. They found that the strongest correlations between the behavioral traits and the resting-state connectome concerned higher-order cognitive abilities[29]. An obvious implication of these findings is that the correlations between brain connectivity and behavior are primarily driven by brain networks that support higher-order cognitive functions. Working memory and its corresponding core brain network represent the logical first candidate because of the known association of WM with multiple higher-order cognitive functions. In order to test this hypothesis, we used sparse canonical correlation analyses (sCCA) to determine the co-variation between brain imaging metrics of WM-network activation and connectivity and non-imaging measures relating to sensorimotor processing, affective and non-affective cognition, mental health and personality, physical health and lifestyle choices derived from 823 HCP participants. We refer to these two datasets as the neuroimaging and the "behavioral-health" dataset.

We chose a sparse multivariate approach because it retains brain regional specificity similar to that seen in region of interest analyses[30] and it does not require data reduction, regardless of the number of subjects and variables and can be used in smaller samples (more typical in neuroimaging studies). We conducted sCCAs at two levels: a global level, testing the overall association between the entire imaging and behavioral-health datasets; and a modular level, testing associations between modules (i.e., subsets) of the two datasets. The purpose of the modular analyses was to facilitate extrapolation of our results to findings available in the literature where similar smaller datasets are the rule. Based on the prior evidence presented above, we hypothesized that imaging and behavioral-health measures will show substantial co-variation revealing the inter-dependent nature of the two datasets; we also hypothesized that correlations would be stronger between neuroimaging and higher-order cognitive function, supporting a key role for the WM-network activation and connectivity.

Materials and Methods

Participants

We used data from the HCP database (http://www.humanconnectome.org) derived from 823 healthy participants (462 women) with a mean age of 29 years (range 22–37 years). All neuroimaging data were acquired on a Siemens Skyra 3T scanner and preprocessed following standard HCP protocols[31]. All the subjects provided informed consent[32]. This study was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai.

HCP behavior and health measures

We used 116 variables corresponding to demographic characteristics, task performance during sensorimotor processing, affective and non-affective cognition, mental health and personality, physical health and lifestyle choices (Supplementary Table 1). For variables with both raw and age-adjusted scores, we selected the age-adjusted measures only. We excluded categorical variables (n=130) where more than 90% of the sample endorsed the same outcome or that were co-linear (r>0.9). For psychometric tests with multiple correlated outcome variables we selected those that are more commonly reported in the literature (see detail in Supplementary information).

WM-network activation

We analyzed fMRI data acquired while participants performed the HCP version of the 2-back task[33] using the Statistical Parametric Mapping software, version 12 (SPM12) (www.fil.ion.ucl.ac.uk/spm/software/spm12/) (details in Supplementary Information). In order to identify WM-related activation, contrast images of the 2-back vs 0-back condition were generated from individual datasets and were then entered into a random-effects group-level one-sample t-test. Suprathreshold clusters were identified at $p<0.05$ with family-wise error correction at voxel level. As expected based on previous literature[3,5], the clusters identified were located bilaterally in the dlPFC, PAR, dACC, the middle temporal gyrus and the visual cortex (VC) (Figure 1). Spherical (radius=4mm) volumes-of-interest (VOIs) were prescribed, centered on the group peak coordinates of each suprathreshold cluster; the radius was chosen to ensure that the VOIs encompassed the individual peak coordinates of all participants. Mean beta values were then extracted and entered in further analyses (Figure 1, Supplementary Table 2).

Functional connectivity of the WM-network

We computed the undirected, model-free functional connectivity of the WM-network from the task-based and resting-state data of each participant. In each dataset, we extracted the average time series of the BOLD signal from the WM-network VOIs described above. Then, we calculated the Fisher-Z transformed Pearson's correlation between each pair of VOIs to create a resting-state and task-related functional connectivity matrix for each individual.

Effective Connectivity

We used Dynamic Causal Modeling (DCM)[34], implemented in the DCM12 toolbox, to estimate the strength of task-specific modulation (2-back vs 0-back) in the connections between the regions of the WM-network. We selected the VOIs in the dlPFC, PAR, dACC and VC, defined as described above based on the results of the second-level analysis (see details in Supplementary Information). This choice was also informed by evidence from meta-analyses[3,5,35] and previous DCM studies of this WM task[17,36]. The time series of the homologous VOIs in each hemisphere were averaged to create a 4-region layout of the WM-network (Supplementary Figure 2A). The coupling of any two VOIs was defined in terms of intrinsic (task-independent) connections while the impact of the WM condition was modeled directly on the VC (driving input) and on the strength of coupling between each pair of VOIs (modulatory input). In addition, we included a non-modulated model (null-model) as a control. Random effects Bayesian model selection was used to compute group-level exceedance and posterior probabilities. Finally, to accommodate any uncertainty about the models, we used random effects Bayesian Model Averaging to obtain average connectivity estimates (weighted by their posterior model probability) across all models and all participants[37].

Sparse Canonical Correlation Analyses

200 imaging and 116 behavioral-health variables were z-standardized and entered into sCCAs implemented using an in-house script[30] (see Supplementary Information). We used the same approach for the global and the modular analyses. For each analysis, we computed the sparse parameters by running the sCCA with a range of candidate values (from 0.1 to 1, at $0.1\times\sqrt{p}$ increments, where p is the number of features in that view of the data) for each imaging and behavioral-health dataset and then fitted the resulting models. We selected the optimal sparse criteria combination based on the parameters that corresponded to the values of the model that maximized the sCCA correlation value. We then computed the optimal

sCCA model and determined its significance using permutations. Accordingly, the imaging dataset was permuted 100,000 times before undergoing the exact same analysis as the original data. The p-value was defined as the number of permutations that resulted in a higher correlation than the original data divided by the total number of permutations. Thus the p-value is explicitly corrected for multiple testing as it is compared against the null distribution of maximal correlation values across all estimated sCCAs. For each permutation we tested all sparsity criteria combinations as for the original data and then extracted the sCCA correlation with the highest coefficient among the tested options, independently of whether this combination was the same as in the original data. In this way we ensured that we did not underestimate the chance of a permutation achieving the same or higher value than the original data. The threshold for statistical significance for each analysis was set at $p<0.05$. When the overall sCCA was significant, we investigated the weight of each variable (on both the imaging and behavioral datasets). To do so, we computed Pearson's correlations between each variable and the mode of the opposing pattern (i.e., each behavioral-health variable to mode of the neuroimaging dataset and vice versa).

Reliability Analyses

First, we tested the effect of potential confounders (sex, intra-cranial volume, acquisition sequence, age) by performing the analysis with and without regressing out these confounds. Second, we confirmed the robustness of the results by randomly resampling half of the sample (n=411) 5000 times and repeating the sCCA each time. Third, we excluded overfitting by using the weights from each of the resampled data and applied them to the other half of the sample. Fourth, we tested whether alternative analyses using CCA would yield the same results. Fifth, to further ensure the robustness of the DCM sCCA results, we tested an alternative DCM model space. Sixth, we tested the specificity of our findings by conducting further analysis examining the association of behavioral-health variables to intrinsic functional connectivity. Seventh, we conducted further analyses to assess whether our results might be influenced by the fact that some HCP participants are related. For more details on all reliability analyses see Supplementary Information and Supplementary Figures 3 and 4.

Results

The overall design of the study is shown in Supplementary Figure 1. The global analysis considered the co-variation of the entire imaging and the entire behavioral-health dataset. Modular analyses examined the co-variation between distinct subsets (i.e., modules) of imaging and behavioral-health data.

Behavioral-Health dataset

We used 116 variables that were considered as a single dataset in the global analysis and as 5 distinct subsets (i.e. modules) corresponding to psychometric measures of sensorimotor processing, affective and non-affective cognition, to mental health and personality, and to physical health and lifestyle choices (Supplementary Table 1).

WM-network activation

Conventional general linear analyses of the fMRI data identified bilateral clusters located in the dlPFC, dACC, PAR, VC and middle temporal gyrus corresponding to the nodes of the 2-back WM-network (Figure 1, Supplementary Table 2). The resulting variables (n=24) comprised the WM activation module (details in Supplementary Information).

Functional connectivity

We computed the functional connectivity of the WM-network based on the results of the second-level analysis described above (and in Supplementary Information). This yielded 66 task-related and 66 resting-state functional connectivity variables comprising the task-related and resting-state functional connectivity module.

Effective Connectivity

We used DCM to specify the strength of intrinsic (task-independent) and WM-modulated connectivity of the WM-network. The exceedance and the posterior probabilities of the models were computed using random effects Bayesian model selection. Bayesian model averaging was used to obtain average connectivity estimates across all models for each participant (details in Supplementary Information, Supplementary Figure 2B–C). This analysis generated 44 DCM measures which comprised the effective connectivity module.

Global Sparse Canonical Correlation Analysis

The global sCCA quantified the relationship between the two sets of measurements comprising 200 neuroimaging variables and 116 behavioral variables. This analysis showed that the two datasets were significantly associated (r=0.50, p=0.00002) (Figure 2A). Amongst the behavioral-health variables, those with the highest correlations (positive or negative) with the imaging variate are shown in Figure 2B (and Supplementary Table 3); they included psychometric measures of fluid intelligence, memory, reading/language, visuospatial orientation, sustained attention, mental flexibility, and emotional recognition; behavioral traits relating to aggression, physical characteristics relating to physical endurance, Body Mass Index (BMI) and Hemoglobin A1c and lifestyle choices (alcohol use and smoking). Variables with positive correlation to the imaging variate represented positive cognitive and physical attributes while negatively correlated variables represented suboptimal health indicators and lifestyle choices. Amongst the imaging variables, metrics of activation were more strongly correlated with the behavioral-health variate (Figure 2C and Supplementary Table 4). Positive correlations were observed with higher activation in the WM-network during the 2-back condition and negative correlations with higher WM-network activation during the sensorimotor control condition; greater effective connectivity between the VC to the dlPFC and PAR also showed positive correlations with the behavioral-health variate while the opposite was the case with regards to increased effective connectivity between the dACC and other WM-network regions (Supplementary Table 4).

Modular Sparse Canonical Correlation Analyses

At this level, sCCAs were implemented to test the co-variation of each neuroimaging module to each of the behavioral modules (Figures 1 and 3; Supplementary Tables 5&6 and

Supplementary Dataset). The results of these analyses largely recapitulated those of the global sCCA. We found that the WM-task activation variate was significantly associated with affective and non-affective cognition, mental health and personality, physical health and lifestyle. The behavioral variables that were most strongly associated with the WM-task activation were fluid intelligence, language, memory and abstraction (non-affective cognition module), facial emotion recognition (affective cognition module), openness (mental health and personality) and physical endurance (physical health and lifestyle). The DCM variate was only associated with the non-affective cognition module (primarily fluid intelligence, language and spatial orientation). Both task and resting-state functional connectivity variates were primarily associated with the physical health and lifestyle module; positive correlations were observed with better endurance, higher hematocrit and sleep quality (as measure in the total score of the Pittsburgh Sleep Questionnaire) while higher BMI as well as high blood pressure and poor glucose control had a detrimental effect. The association between physical health measures was not specific to the WM-network as it was also observed in connection to whole-brain functional connectivity (details in Supplementary information).

Reliability analyses

For the global analysis, half of the sample (n=411) was randomly resampled 5000 times. sCCAs repeated each time resulted in a mean r-value=0.53 (standard-deviation=0.04). We used the weights of each sCCA permutation to the respective 5000 sets of the remaining half of the sample. These scores yielded a mean r-value=0.39 (standard-deviation=0.06). For the modular analyses, no difference above two standard deviations was found between the averaged resampled data and the actual data, for any of the significant models (Supplementary Table 7), confirming the reliability of the present results. The sCCA results were virtually unchanged regardless of whether we regressed out or stratified the analysis to account for intra-cranial volume, acquisition sequence, sex and age. We use sex to illustrate this; as shown in Supplementary Information (Supplementary Table 8), no differences were found in the global analysis between the main results and results of separate sCCAs for men (n=361) and women (n=462). Lastly, the results remained unchanged when we used alternative definitions of the DCM model space, when we computed regular CCAs instead of sCCAs (Supplementary Table 9) and when accounting for family structure (details for all these analyses in Supplementary Information).

Discussion

We used the rich dataset of the Human Connectome Project to quantify brain-behavior co-variation relevant to working memory. We found that cognitive measures reflecting better general intellectual ability, visuospatial skills, language, attention and mental flexibility, were amongst the behavioral measures with the strongest positive correlations to imaging phenotypes indexing WM-network function. By contrast, variables relating to aggression, substance use and suboptimal cognition were amongst the behavioral measures with the strongest negative correlations to imaging phenotypes indexing WM-network function.

Fluid intelligence had the strongest positive correlation with neuroimaging phenotypes of WM function both in the global and modular analyses. This observation significantly enhances our understanding of the relationship between fluid intelligence and WM, a topic that has been debated for nearly three decades[38]. We show that even when multiple other variables are taken into account, fluid intelligence remains strongly correlated with WM-network functional integrity. This suggests that both cognitive constructs are supported by common neural mechanisms. The close link between intelligence and WM is further supported by a recent study that examined individual variability in functional brain connectivity[39]; the WM-network connectome had the most distinctive fingerprint at the individual level and was the most significant predictor of fluid intelligence[39]. Consistent with the notion that the WM-network identified via the 2-back task has a domain-general role[18,19], we found that WM-network activation and effective connectivity were associated with a wide range of higher-order functions relating to executive control of attention, visual orientation and language (see also Supplementary Discussion).

The global and modular analyses identified several lifestyle choices and physical traits that showed significant covariation with WM-network imaging metrics. Amongst lifestyle choices, alcohol binge drinking and regular weekly smoking were negatively correlated with WM-network function. Alcohol-related WM dysfunction across the lifespan has been amply documented in prior literature[40,41] and is further supported by the current study. Nicotine enhances attention and cognition, including WM[42], in a baseline-dependent fashion such that individuals with lower baseline function benefit the most from nicotine use[43]. This mechanism has been proposed to explain initiation and maintenance of smoking. It is therefore possible that the negative correlation between weekly smoking levels and WM-network function reflects lower baseline WM-network function in smokers. Alternatively, nicotine abstinence in smokers leads to reduced WM performance compared to non-smokers[44] and is associated with lower BOLD signal in the fronto-parietal WM-network regions[45]. Our results may therefore reflect some aspect of abstinence-related WM-network dysfunction, as access to nicotine is restricted during scanning. Better physical endurance was positively associated with WM-network activation and connectivity. Conversely, suboptimal blood pressure and glucose control and higher BMI had a negative effect on functional connectivity. This close dependency between physical traits and task-related brain activation, connectivity and resting-state connectivity is not specific to WM as it was also observed in connection to whole-brain resting-state connectivity as shown in our supplemental analyses. The same correlation pattern has also been reported in data from the 5000 participants of the UKBiobank[46] and is likely to reflect the fact that these imaging metrics are directly derived from changes in the hemodynamic brain responses and seem sensitive to cardiometabolic factors that may affect blood oxygenation. These observations are of potential translational value in view of recent studies[47,48] showing that increased physical activity could improve WM-related performance and brain phenotypes. In addition, the role of physical traits and lifestyle choices for WM-network function bolsters arguments for accounting for these variables when using neuroimaging to examine clinical populations prior to making inferences about specific-disease related mechanisms[28].

Age made a limited contribution to the results, which is likely due to the restricted age range of the HCP participants. There was no effect of sex on the sCCA models which is in line with previous reports, that unlike other aspects of brain structure and function, the WM-network may not be sexually dimorphic[21,49].

Our study has several limitations. The 2-back task does not isolate possibly distinctive components of WM (e.g., goal maintenance, storage capacity, interference control). It is therefore possible that the multifactorial nature of the 2-back task may lead to greater overlap with fluid intelligence than might be the case with other paradigms that map onto specific WM component (e.g., oculomotor delayed response[37] and Sternberg spatial memory tasks[40] that dissociate encoding and maintenance processes). Neuroimaging techniques include other modalities (such as diffusion weighted imaging and magnetic resonance spectroscopy) and other analytic methods (such as graph theory and dynamic connectivity) that were not considered here. Nevertheless, our study examined those modalities and analytical methods that are most commonly used in neuroimaging studies of WM. Finally, the correlational nature of the analyses does not resolve causality, but the results are still important as they identify modifiable potential risk-factors for WM dysfunction.

In conclusion, we describe a brain-behavior model for WM which demonstrates a positive association between WM-network function with variables reflecting better cognitive abilities and physical well-being while the opposite was the case for indicators of suboptimal health and substance use. We confirm that the WM network is closely linked to general intellectual ability and acts as a domain-general network to support multiple higher-order cognitive functions. The dependency of neuroimaging phenotypes on behavioral-health measures suggests that such factors should be considered as potential confounds in clinical studies and as modifiable targets could inform personalized interventions and public health efforts for the promotion of mental well-being.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Dr. Jakob Heinzle and Dr. Klaas Enno Stephan, of the Translational Neuromodeling Unit, University of Zurich and ETH Zurich, Switzerland for their help with the study. This work was supported in part through the computational resources and staff expertise provided by Scientific Computing at the Icahn School of Medicine at Mount Sinai. Dr. Frangou received support from the National Institutes of Health (R01 MH104284-01A1) and European Unit FP7 program (IMAGEMEND 602450; IMAging GEnetics for MENtal Disorders) projects. Dr. Moser received support from the Swiss National Science Foundation (P2GEP3_162104, P300PB_171584). Dr. Schuman and Dr. Ing are partially supported by IMAGEMEND (602450); the National Institute for Health Research (NIHR; Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London) and the Bundesministerium für Bildung und Forschung (eMED SysAlc01ZX1311A). Dr. Dima was partially supported by a NARSAD 2014 Young Investigator Award (Leichtung Family Investigator, Grant ID: 22471) and a Psychiatric Research Trust (Grant Reference: 92 Branthwaite) grant. Data collection and sharing for this project was provided by the MGH-USC Human Connectome Project (NIH 1U54MH091657, http://www.humanconnectome.org/; Principal Investigators: Bruce Rosen, M.D., Ph.D., Arthur W. Toga, Ph.D., Van J. Weeden, MD). HCP funding was provided by the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Mental Health (NIMH), and the National Institute of Neurological Disorders and Stroke (NINDS). HCP data are disseminated by the Laboratory of Neuro Imaging at the University of California, Los Angeles.

References

1. Baddeley A. Working memory: theories, models, and controversies. Annu Rev Psychol. 2012; 63:1–29. [PubMed: 21961947]
2. Diamond A. Executive functions. Annu Rev Psychol. 2013; 64:135–168. [PubMed: 23020641]
3. Fletcher PC, Henson RN. Frontal lobes and human memory: insights from functional neuroimaging. Brain. 2001; 124(Pt 5):849–881. [PubMed: 11335690]
4. Owen AM, Herrod NJ, Menon DK, Clark JC, Downey SP, Carpenter TA, et al. Redefining the functional organization of working memory processes within human lateral prefrontal cortex. Eur J Neurosci. 1999; 11(2):567–574. [PubMed: 10051756]
5. Wager TD, Smith EE. Neuroimaging studies of working memory: a meta-analysis. Cogn Affect Behav Neurosci. 2003; 3(4):255–274. [PubMed: 15040547]
6. D'Esposito M, Postle BR, Rypma B. Prefrontal cortical contributions to working memory: evidence from event-related fMRI studies. Exp Brain Res. 2000; 133(1):3–11. [PubMed: 10933205]
7. Narayanan NS, Prabhakaran V, Bunge SA, Christoff K, Fine EM, Gabrieli JD. The role of the prefrontal cortex in the maintenance of verbal working memory: an event-related FMRI analysis. Neuropsychology. 2005; 19(2):223–232. [PubMed: 15769206]
8. Guerin SA, Miller MB. Parietal cortex tracks the amount of information retrieved even when it is not the basis of a memory decision. Neuroimage. 2011; 55(2):801–807. [PubMed: 21126590]
9. Jonides J, Schumacher EH, Smith EE, Koeppe RA, Awh E, Reuter-Lorenz PA, et al. The role of parietal cortex in verbal working memory. J Neurosci. 1998; 18(13):5026–5034. [PubMed: 9634568]
10. Carter CS, Botvinick MM, Cohen JD. The contribution of the anterior cingulate cortex to executive processes in cognition. Rev Neurosci. 1999; 10(1):49–57. [PubMed: 10356991]
11. Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC. A parametric study of prefrontal cortex involvement in human working memory. Neuroimage. 1997; 5(1):49–62. [PubMed: 9038284]
12. Callicott JH, Mattay VS, Bertolino A, Finn K, Coppola R, Frank JA, et al. Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. Cereb Cortex. 1999; 9(1):20–26. [PubMed: 10022492]
13. Volle E, Kinkingnehun S, Pochon JB, Mondon K, Thiebaut de Schotten M, Seassau M, et al. The functional architecture of the left posterior and lateral prefrontal cortex in humans. Cereb Cortex. 2008; 18(10):2460–2469. [PubMed: 18308710]
14. Braun U, Schafer A, Walter H, Erk S, Romanczuk-Seiferth N, Haddad L, et al. Dynamic reconfiguration of frontal brain networks during executive cognition in humans. Proc Natl Acad Sci U S A. 2015; 112(37):11678–11683. [PubMed: 26324898]
15. Sala-Llonch R, Pena-Gomez C, Arenaza-Urquijo EM, Vidal-Pineiro D, Bargallo N, Junque C, et al. Brain connectivity during resting state and subsequent working memory task predicts behavioural performance. Cortex. 2012; 48(9):1187–1196. [PubMed: 21872853]
16. Friston KJ. Functional and effective connectivity: a review. Brain Connect. 2011; 1(1):13–36. [PubMed: 22432952]
17. Dima D, Jogia J, Frangou S. Dynamic causal modeling of load-dependent modulation of effective connectivity within the verbal working memory network. Hum Brain Mapp. 2014; 35(7):3025–3035. [PubMed: 24142432]
18. Kane MJ, Conway ARA, Hambrick DZ, Engle RW. Variation in working memory capacity as variation in executive attention and control. In: Conway ARA, Jarrold C, Kane MJ, Miyake A, Towse JN, editorsVariation in working memory. Oxford University Press; New York: 2007
19. Engle RW, Kane MJ. Executive attention, working memory capacity and two-factor theory of cognitive control In: Ross B (ed) The Psychology of Learning and Motivation. Elsevier; New York: 2004. 145–199.
20. Dima D, Friston KJ, Stephan KE, Frangou S. Neuroticism and conscientiousness respectively constrain and facilitate short-term plasticity within the working memory neural network. Hum Brain Mapp. 2015; 36(10):4158–4163. [PubMed: 26189566]

21. Hill AC, Laird AR, Robinson JL. Gender differences in working memory networks: a BrainMap meta-analysis. Biol Psychol. 2014; 102:18–29. [PubMed: 25042764]
22. Rannikko I, Jaaskelainen E, Miettunen J, Ahmed AO, Veijola J, Remes AM, et al. Predictors of Long-Term Change in Adult Cognitive Performance: Systematic Review and Data from the Northern Finland Birth Cohort 1966. Clin Neuropsychol. 2016; 30(1):17–50. [PubMed: 26734714]
23. Wang M, Gamo NJ, Yang Y, Jin LE, Wang XJ, Laubach M, et al. Neuronal basis of age-related working memory decline. Nature. 2011; 476(7359):210–213. [PubMed: 21796118]
24. Tempest GD, Davranche K, Brisswalter J, Perrey S, Radel R. The differential effects of prolonged exercise upon executive function and cerebral oxygenation. Brain Cogn. 2017; 113:133–141. [PubMed: 28235695]
25. Gottesman RF, Schneider AL, Albert M, Alonso A, Bandeen-Roche K, Coker L, et al. Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. JAMA Neurol. 2014; 71(10):1218–1227. [PubMed: 25090106]
26. Matthews BR. Memory dysfunction. Continuum (Minneap Minn). 2015; 21:613–626. 3 Behavioral Neurology and Neuropsychiatry. [PubMed: 26039844]
27. Millan MJ, Agid Y, Brune M, Bullmore ET, Carter CS, Clayton NS, et al. Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nat Rev Drug Discov. 2012; 11(2):141–168. [PubMed: 22293568]
28. Weinberger DR, Radulescu E. Finding the Elusive Psychiatric “Lesion” With 21st-Century Neuroanatomy: A Note of Caution. Am J Psychiatry. 2016; 173(1):27–33. [PubMed: 26315983]
29. Smith SM, Nichols TE, Vidaurre D, Winkler AM, Behrens TE, Glasser MF, et al. A positive-negative mode of population covariation links brain connectivity, demographics and behavior. Nat Neurosci. 2015; 18(11):1565–1567. [PubMed: 26414616]
30. Witten DM, Tibshirani R, Hastie T. A penalized matrix decomposition, with applications to sparse principal components and canonical correlation analysis. Biostatistics. 2009; 10(3):515–534. [PubMed: 19377034]
31. Glasser MF, Sotiropoulos SN, Wilson JA, Coalson TS, Fischl B, Andersson JL, et al. The minimal preprocessing pipelines for the Human Connectome Project. Neuroimage. 2013; 80:105–124. [PubMed: 23668970]
32. Van Essen DC, Barch DM. The human connectome in health and psychopathology. World Psychiatry. 2015; 14(2):154–157. [PubMed: 26043324]
33. Barch DM, Burgess GC, Harms MP, Petersen SE, Schlaggar BL, Corbetta M, et al. Function in the human connectome: task-fMRI and individual differences in behavior. Neuroimage. 2013; 80:169–189. [PubMed: 23684877]
34. Friston KJ, Harrison L, Penny W. Dynamic causal modelling. Neuroimage. 2003; 19(4):1273–1302. [PubMed: 12948688]
35. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp. 2005; 25(1):46–59. [PubMed: 15846822]
36. Dima D, Roberts RE, Frangou S. Connectomic markers of disease expression, genetic risk and resilience in bipolar disorder. Transl Psychiatry. 2016; 6:e706. [PubMed: 26731443]
37. Chafee MV, Goldman-Rakic PS. Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. J Neurophysiol. 1998; 79(6):2919–2940. [PubMed: 9636098]
38. Kyllonen PC, Christal RE. Reasoning ability is (little more than) working-memory capacity? Intelligence. 1990; 14(4):389–433.
39. Finn ES, Shen X, Scheinost D, Rosenberg MD, Huang J, Chun MM, et al. Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity. Nat Neurosci. 2015; 18(11):1664–1671. [PubMed: 26457551]
40. Mayhugh RE, Moussa MN, Simpson SL, Lyday RG, Burdette JH, Porrino LJ, et al. Moderate-Heavy Alcohol Consumption Lifestyle in Older Adults Is Associated with Altered Central Executive Network Community Structure during Cognitive Task. PLoS One. 2016; 11(8):e0160214. [PubMed: 27494180]

41. Silveri MM, Dager AD, Cohen-Gilbert JE, Sneider JT. Neurobiological signatures associated with alcohol and drug use in the human adolescent brain. Neurosci Biobehav Rev. 2016; 70:244–259. [PubMed: 27377691]

42. Heishman SJ, Kleykamp BA, Singleton EG. Meta-analysis of the acute effects of nicotine and smoking on human performance. Psychopharmacology (Berl). 2010; 210(4):453–469. [PubMed: 20414766]

43. Niemegeers P, Dumont GJ, Quisenaerts C, Morrens M, Boonzaier J, Fransen E, et al. The effects of nicotine on cognition are dependent on baseline performance. Eur Neuropsychopharmacol. 2014; 24(7):1015–1023. [PubMed: 24766971]

44. Grundey J, Amu R, Ambrus GG, Batsikadze G, Paulus W, Nitsche MA. Double dissociation of working memory and attentional processes in smokers and non-smokers with and without nicotine. Psychopharmacology (Berl). 2015; 232(14):2491–2501. [PubMed: 25721074]

45. McClernon FJ, Froeliger B, Rose JE, Kozink RV, Addicott MA, Sweitzer MM, et al. The effects of nicotine and non-nicotine smoking factors on working memory and associated brain function. Addict Biol. 2016; 21(4):954–961. [PubMed: 25904425]

46. Miller KL, Alfaro-Almagro F, Bangerter NK, Thomas DL, Yacoub E, Xu J, et al. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nat Neurosci. 2016; 19(11):1523–1536. [PubMed: 27643430]

47. Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci. 2008; 9(1):58–65. [PubMed: 18094706]

48. Felez-Nobrega M, Hillman CH, Cirera E, Puig-Ribera A. The association of context-specific sitting time and physical activity intensity to working memory capacity and academic achievement in young adults. Eur J Public Health. 2017

49. Schmidt H, Jogia J, Fast K, Christodoulou T, Haldane M, Kumari V, et al. No gender differences in brain activation during the N-back task: an fMRI study in healthy individuals. Hum Brain Mapp. 2009; 30(11):3609–3615. [PubMed: 19387979]

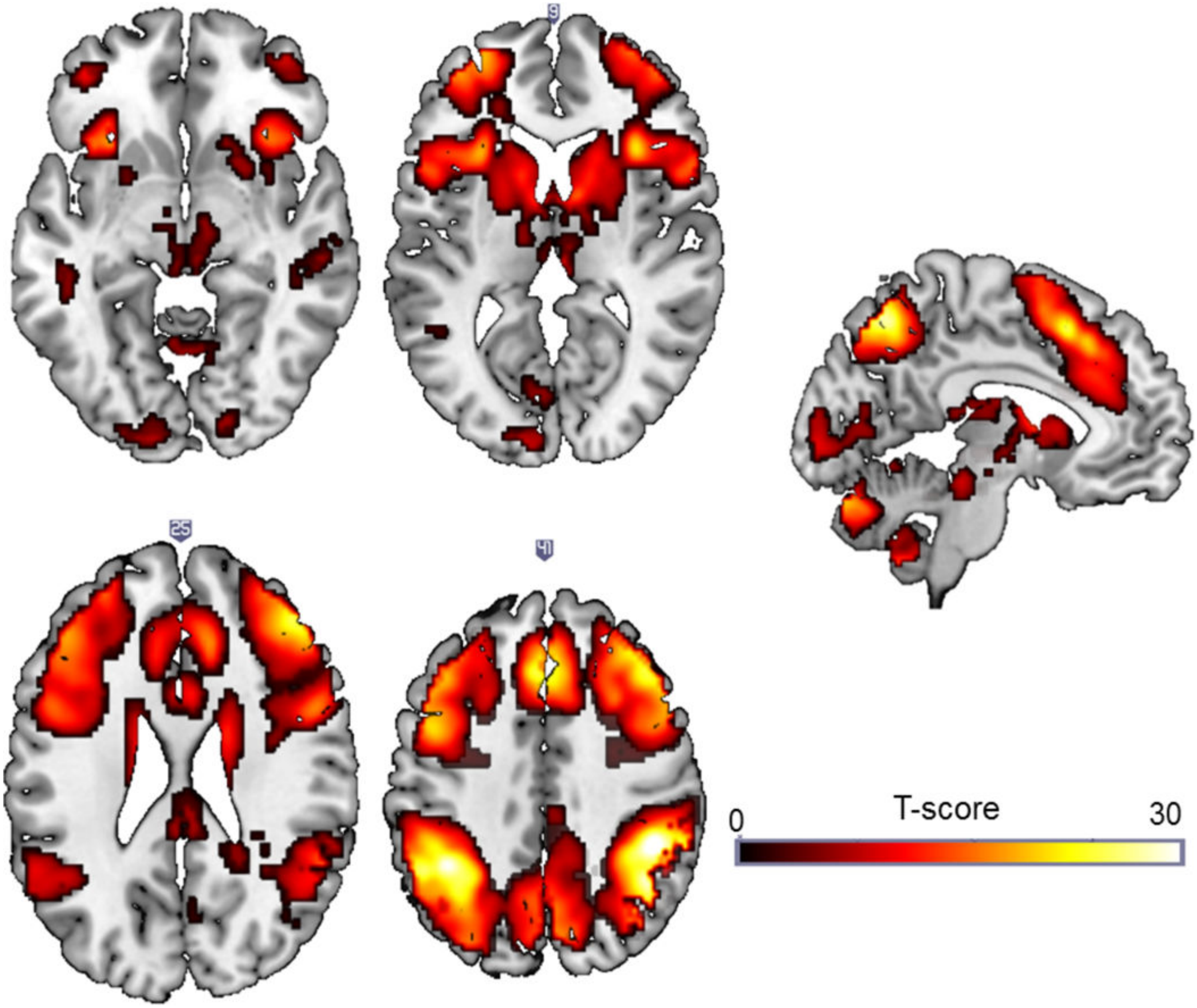
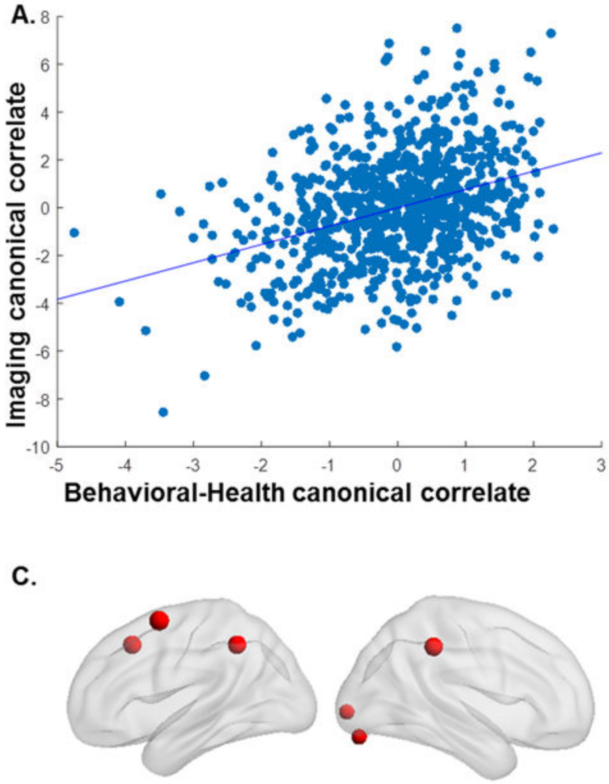


Figure 1.
Suprathreshold clusters of activation in the 2-back task. Data derived from the entre sample (n=823); p<0.05 with familywise error (FWE) voxelwise correction and minimum k=30 voxels.



B. Behavioral-Health Variables	r-value
Penn Progressive Matrices (Fluid Intelligence)	0.41
Reading Recognition	0.33
Spatial Orientation (Line Orientation)	0.32
Picture Vocabulary Test	0.29
List Sorting (Working Memory Test)	0.26
Picture Sequence Memory Test	0.24
Dimensional Card Sorting Test (Cognitive Flexibility)	0.22
Sustained Attention (Specificity)	0.19
Emotion Recognition	0.18
Physical Endurance	0.17
Thought Problems	-0.09
Aggressive Behavior	-0.09
Hemoglobin A1C	-0.10
Conscientiousness	-0.10
Times Drunk Last Year	-0.11
Body Mass Index	-0.12
Weekly Tobacco Use	-0.15
Continuous Attention (False positives)	-0.19
Errors Line Orientation	-0.32
Skipped Items Penn Progressive Matrices	-0.39

Figure 2. Global sparse canonical correlation analysis

A. Significant correlation between all imaging and behavioral-health variates (n=823, r=0.50, p-value=0.00002). **B.** Top behavioral-heath variables the most strongly associated with the imaging variate. **C.** Top WM-network activation variables positively associated with the behavioral-health variate. The size of the sphere represents the degree of correlation.

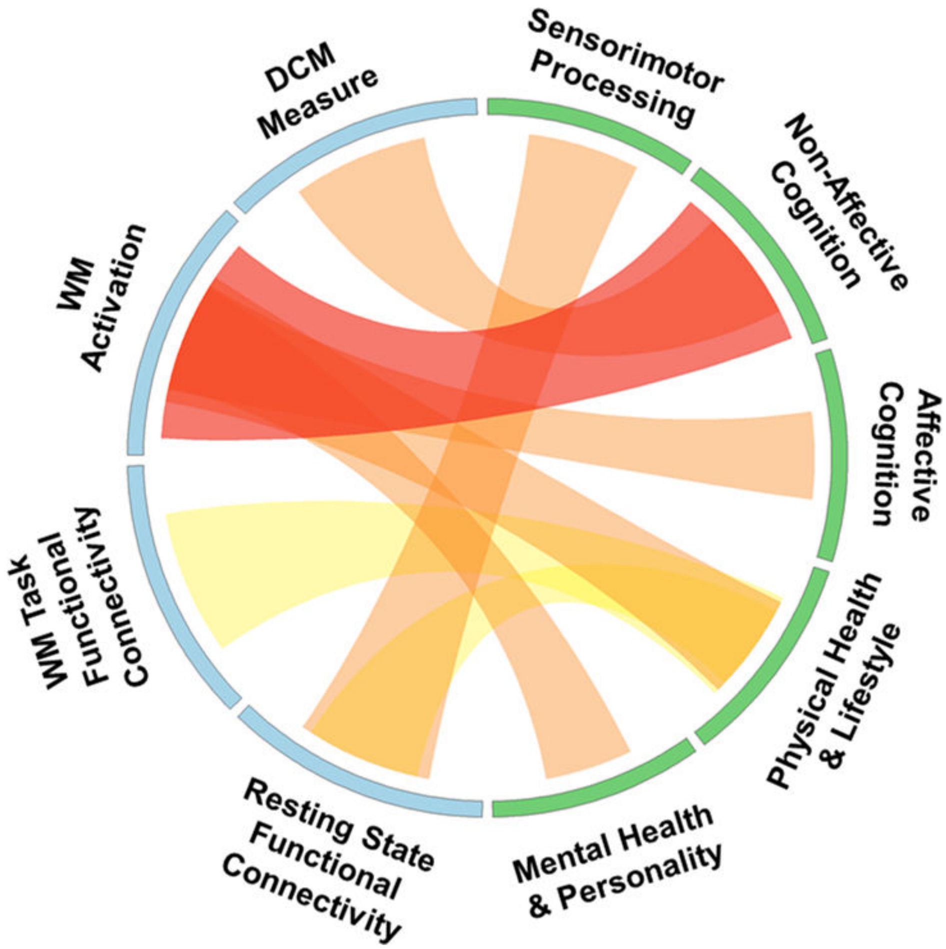


Figure 3. Modular sparse canonical correlation analysis

The connections between the modules are sized based on the r-values. *Yellow* connections indicate significant associations at p<0.05; *Orange* connections indicate significant associations at p<0.01; *Red* connections indicate significant associations at p<0.001.